Paper No. 43

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte THOMAS WALDMANN

Appeal No. 2002-1930
Application No. 08/478,748

ON BRIEF

Before ADAMS, SCHEINER and MILLS, Administrative Patent Judges.

MILLS, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. §134 from the examiner's final rejection of claim 27, the only claim pending in this application.

Claim 27 on appeal and reads as follows:

27. A method for reducing levels of Tac-positive cells in patients with elevated levels of Tac-positive cells comprising the steps of,

a) determining a dosage, said dosage comprising 5 -15 mCi ^{90}Y-conjugated anti-Tac in a total amount of 2-20 mg anti-Tac, wherein the dose is 2 mg total anti-Tac if said patient has sIL-2R levels of less than 2000 units/ml, the dose is 5 mg total anti-Tac if said patient has sIL-2R levels of 2,000 - 10,000 units/ml, the dose is 10 mg of total anti-Tac if the patient has sIL-2R levels of 10,000 - 50,000 units/ml, and the dose is 20 mg of total anti-Tac if said patient has sIL-2R of greater than 50,000 units/ml; and

b) administering said dosage to said patient to eliminate disease associated Tac-positive cells.

The prior art references relied upon by the examiner are:

Waldmann, et al. (Waldmann 1), "The Interleukin-2 Receptor: A Target for Monoclonal Antibody Treatment of Human T-cell Lymphotropic Virus I-Induced Adult T-Cell Leukemia, Blood, Vol. 82, No. 6, pp. 1701-1712 (1993)

Waldmann et al. (Waldmann 2), "Anti-IL-2 Receptor Monoclonal Antibody (Anti-Tac) Treatment of T-Cell Lymphoma 8," Imp. Adv. in Onc., pp. 131-141 (1994)

Waldmann et al. (Waldmann 3), "1992 Stohlman Memorial Lecture: Targeting the IL-2 Receptor," Leukemia, Vol. 7, (Suppl 2), pp. s151-s156 (1993)

Waldmann et al. (Waldmann 4), "Lymphokine receptors: A target for immunotherapy of lymphomas," Annals of Oncology, Vol. 5 (Suppl 1), pp. s13-s17 (1994)

Waldmann et al. (Waldmann 5), "Radioimmunotherapy of Interleukin-2Rα- Expressing Adult T-Cell Leukemia with Yttrium-90-Labeled Anti-Tac, Blood, Vol. 86, No. 11, pp. 4063-4075 (1995)

Vriesendorp et al. (Vriesendorp), "Review of Five Consecutive Studies of Radiolabeled Immunoglobulin Therapy in Hodgkin's Disease," Cancer Research, (Suppl.) 55, pp. 5888s-5892s (1995)

Rubin et al. (Rubin), "The Soluble Interleukin-2 Receptor: Biology, Function and Clinical Application, Annals of Internal Medicine, Vol. 13, No. 8, pp. 619-627 (1990)

Grounds of Rejection

Claim 27 stands rejected under 35 U.S.C. 102(b) for anticipation in view of Waldmann 1 as evidenced by Waldmann 5 and/or Vriesendorp, or in the alternative claim 27 stands rejected for obviousness under 35 U.S.C. 103(a) in view of these references.

Claim 27 stands rejected under 35 U.S.C. 103(a) for obviousness over Waldmann 1 and/or Waldmann 2 and/or Waldmann 3 Leukemia, and/or Waldmann 4 in view of Vriesendorp and Rubin.

We reverse these rejections.

DISCUSSION

Background

Based upon in vivo pharmacokinetic and bioavailability studies during the Phase I trial using ^{90}Y- anti-Tac the specification indicates that "an algorithm to predict a dose of total anti-Tac (sum in mg of unlabeled and labeled antibody) that was sufficient to overcome the effect of soluble antigen levels (i.e., sIL-2R), without excessively diluting antibody-specific activity"[1] was developed Specification, page 14.

Factors that appear to be critical in developing an effective radioimmuno-therapeutic regimen include (a) the choice of radionuclide; (b) the selection of the chelate used to link the radionuclide to the monoclonal antibody; (c) the choice of monoclonal antibody; and (d) the definition of optimal quantity of monoclonal antibody to be administered. Specification, page 14.

^{90}Y is diclosed in the specification to be an attractive choice for therapy of lymphoma since it decays with high-energy beta but no gamma emissions. The energy

---

[1] Specific activity is defined as the activity of a radioelement per unit weight of element or the activity per unit mass of a pure radionuclide. Hawley's Condensed Chemical Dictionary, John Wiley & Sons, New York, p. 1038 (1997) [attached]

released per unit activity of is approximately five times greater than that of ^{131}I and would yield a significantly higher radiation dose delivered to the tumor. The high-energy beta emission of ^{90}Y may be of specifical value for large tumors, including malignant lymph nodes, because this emission manifests greater tissue penetration than low-energy beta emission of ^{131}I. Therefore, ^{90}Y-labeled monoclonal antibodies can kill nontargeted antigen-nonexpressing tumor cells through a "crossfire" effect from neighboring antigen-expressing cells that have been targeted by the radiolabeled monoclonal antibody. Specification, page 15.

An additional factor that is critical in the design of effective therapeutic trials concerns the definition of quantity of administered antibody (sum of radiolabeled and unmodified antibody) that delivers the highest proportion of the administered radiolabeled monoclonal antibody to the surface of the target cells, in the present case, IL-2R cells. This is not achieved by administering the radiolabeled antibody at the highest possible specific activity, nor is it achieved by administering sufficient monoclonal antibody to saturate all receptor targets. Specification, page 17.

When small quantities of radiolabeled antibody were administered to patients with high sIL-2Rα levels, the administered radiolabeled antibodies formed complexes with circulating sIL-2R and were no longer able to bind to target tumor cells efficiently. At the other extreme, if a large total quantity of antibody is administered, the tumor cell surface receptor sites become saturated and much of the radiolabeled antibody remains in the plasma and other extracellular body fluids unbound to the tumor cells,

thereby reducing the proportion of the administered radioactivity delivered to the tumor cell and increasing the radiation delivered to normal tissues. Specification, page 18.

The present invention "derived a relationship to predict a dose of total anti-Tac in milligrams that is sufficient to overcome the blockade to tumor cell binding caused by circulating specific soluble antigen (sIL-2R) levels, yet does not dilute the antibody radioactivity excessively, thereby yielding a therapeutic regimen with improved antibody bioactivity, cell binding, and targeting of radioactivity to tumor for imaging and therapy." Specification, page 18.

35 U.S.C. § 102(b)/103

Claim 27 stands rejected under 35 U.S.C. 102(b) for anticipation in view of Waldmann 1 as evidenced by Waldman 5 or Vriesendorp. Claim 27 alternatively stands rejected under 35 U.S.C. 103(a) for obviousness over these references.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." Verdegaal Bros., Inc. v. Union Oil Co., 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "It is also an elementary principle of patent law that when, as by a recitation of ranges or otherwise, a claim covers several compositions, the claim is 'anticipated' if one of them is in the prior art." Titanium Metals Corp. of America v. Banner, 778 F.2d 775, 782, 227 USPQ 773, 779 (Fed. Cir. 1985).

According to the examiner (Answer, page 3):

> Waldmann et al. [Waldmann 1] teach administering 5 - 15 mCi doses of ^{90}Yttrium (^{90}Y) - labeled anti-Tac antibody ... to achieve remission in treating adult T cell leukemia (ATL) patients in a dose-escalation trial (see page 1711, column 1, paragraph 1 of Waldmann, Blood 1993) including the determination of soluble IL-2 receptor (IL-2R) levels, encompassed by the claimed methods... The claimed functional limitations would be inherent properties of the referenced therapeutic modalities.

The examiner additionally argues that the evidentiary references Waldmann 5 and Vriesendorp have been provided to support the inherency of prior art teachings in Waldmann 1 of administering 5 - 15 mCi doses of ^{90}Y labeled anti-Tac antibody to achieve remission in patients with adult T cell leukemia. Id. The examiner particularly points to discussion in Waldmann 1, page 1711, column 1, paragraph 1. This passage of Waldmann 1 states:

> To improve the effectiveness of IL-2R-directed therapy of ATL during the late phase of this disease, different approaches were initiated to arm anti-Tac to augment its cytotoxic activity. ... For example, we bound β-emitting ^{90}Y to anti-Tac using chelates that did not permit elution of radiolabeled yttrium from the monoclonal antibody. ....[W]e initiated a dose-escalation trial with ^{90}Y-labeled anti-Tac for the treatment of ATL. At the 5 - to 15 mCi doses used, 10 of 15 patients underwent a partial (eight patients) or complete (two patients) remission...

Appellant argues that Waldmann 1 describes the use of *unlabeled* anti-Tac in patients with adult T-cell leukemia (ATL). Brief, pages 8-9. Appellant also argues that Waldmann 1 teaches that it is preferred to use a 50 mg. anti-Tac dose, in order to saturate IL-2R. Brief, pages 9-10. Importantly, appellant argues that the claimed method requires a step of determining a dosage and administering the dosage to the patient to eliminate the disease-associated Tac-positive cells which is not taught in Waldmann 1. Brief, pages 7-8. Appellant argues that nothing in Waldmann 1 teaches

or suggests the use of anti-Tac at doses less than the 20-50 mg described in the Waldmann 1. To summarize, appellant argues that the examiner has engaged in hindsight reconstruction of appellant's invention and that the secondary references do not establish the inherency of the step of determining the claimed dosage amounts. Brief, pages 10-11.

While we disagree with appellant that Waldmann 1 only describes the administration of dosages of unlabeled anti-Tac (Waldmann 1 also describes the administration of ^{90}Y-labeled anti-Tac), we agree with appellant that the examiner has failed to established a prima facie case of anticipation based upon the doctrine of inherency as evidenced by Waldmann 5 and Vriesendorp.

The examiner has pointed to the particular location in Waldmann 1 for the administration of ^{90}Y labeled anti-Tac for the treatment of ATL. This passage does not disclose the claimed method step of determining an appropriate dosage of ^{90}Y labeled anti-Tac as set forth in claim 27. The examiner tries to make up for this deficiency citing Waldmann 5 and Vriesendorp. Vriesendorp describes the treatment of Hodgkin's disease with dosages of ^{90}Y labeled antiferritin. We do not find the dosages provided for antiferritin (a protein unrelated to anti-Tac), to be relevant to the claimed subject matter before us.

As to Waldmann 5, the examiner argues that the clinical trial described in Waldmann 1 "led to the dosing algorithm described in Waldmann 5 which reads on a determination of a dosing regimen of administering ^{90}Y labeled anti-Tac antibody at

different dosages based upon a patients' soluble IL-2R levels." Answer, page 10. We disagree with the examiner that the later described and determined algorithm of Waldmann 5 can be used to show inherency of the claimed dosing determination step at the time of the Waldmann 1 publication. At best, Waldmann 1 describes a dose escalation study based on escalating radiation doses of ^{90}Y. Nothing is reported in Waldmann 1 regarding an appropriate anti-Tac dose in mg or how to determine varying dosages based on a correlation of a patients sIL-2R levels to ^{90}Y labeled anti-Tac antibody mg amounts, as described in the specification and set forth in claim 27.

The examiner additionally argues that "it is not necessary that the prior art provide all of the dosages and amounts of ^{90}Y conjugated anti-Tac antibody..." "The prior art does not have to meet each asserted level, provided it meets one of the ranges of ^{90}Y anti-Tac antibody/soluble IL-2R levels." Answer, pages 7-8. However, the examiner has not indicated where, and we do not find where Waldmann 1 has provided any mg dosage of ^{90}Y- anti-Tac antibody or indicated a specific method for determining an appropriate dosage based on IL-2R levels. Moreover, the claims require more than the administration of a specific dosage, the claims require a method step of determining a dosage based on a predetermined sIL-2R level and then administering the determined dosage, which as we understand, the claimed invention may include both ^{90}Y-labeled anti-Tac antibodies and unlabeled anti-Tac antibodies, in accordance with that level. Thus, in our view, Waldmann 1 does not explicitly or inherently describe a method of dosage determination suggesting a correlation between dosage of ^{90}Y

labeled anti-Tac and soluble IL-2R levels and a step of determining an appropriate dosage of total antibody (both labeled and unlabeled), as claimed. Vriesendorp does not make up for this deficiency, nor does Waldmann 5.

For at least this reason, the rejection of the claims for anticipation over Waldmann 1 as evidence by Waldmann 5 or Vriesendorp is reversed. For similar reasons, we do not find that the cited combination of references supports a rejection of the claims for obviousness under 35 U.S.C. § 103(a).

35 U.S.C. 103(a)

Claim 27 stands rejected under 35 U.S.C. 103(a) for obviousness over Waldmann 1 and/or Waldmann 2 and/or Waldmann 3, and/or Waldmann 4 in view of Vriesendorp and Rubin.

In rejecting claims under 35 U.S.C. § 103, the examiner bears the initial burden of presenting a prima facie case of obviousness. See In re Rijckaert, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993). It is well-established that the conclusion that the claimed subject matter is prima facie obvious must be supported by evidence, as shown by some objective teaching in the prior art or by knowledge generally available to one of ordinary skill in the art that would have led that individual to combine the relevant teachings of the references to arrive at the claimed invention. See In re Fine, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988).

It is the examiner's position that (Answer, page 13):

> the prior art Waldmann references all teach a dose escalation clinical trial of administering 5- 15 mCi ^{90}Y labeled anti-Tac antibody to achieve remission in treating adult T-cell leukemia (ATL) and that it was known at the time the invention was made that the serum concentrations of the soluble form of IL-2Rα was elevated in patients with disorders encompassing lymphoid neoplasia, select autoimmune diseases and in individuals rejecting allografts.

As indicated in the discussion above, we do not find the disclosure of Vriesendorp relating to the administration of unrelated antiferritin to be relevant to a method of determining a dosing for ^{90}Y labeled anti-Tac antibody. Nor do we agree that Rubin, generally describing that certain sIL-2R levels have been found to be present in particular disease states, makes up for the deficiencies of the Waldmann references and their failure to particularly describe the claimed step of determining a dosage, said dosage comprising 5 -15 mCi ^{90}Y-conjugated anti-Tac in a total amount of 2-20 mg anti-Tac, wherein the dose is 2 mg total anti-Tac if said patient as sIL-2R levels of less than 2000 units/ml, the dose is 5 mg total anti-Tac if said patient has sIL-2R levels of 2,000 - 10,000 units/ml, the dose is 10 mg of total anti-Tac if the patient has sIL-2R levels of 10,000 - 50,000 units/ml, and the dose is 20 mg of total anti-Tac if said patient as sIL-2R of greater than 50,000 units/ml.

We find it unnecessary to reach the Declaration of Dr. Waldmann filed March 2, 1999, in view of the failure of the examiner to establish a prima facie case of obviousness over the cited references.

The rejection of the claims for obviousness over Waldmann 1 and/or Waldmann 2 and/or Waldmann 3, and/or Waldmann 4 in view of Vriesendorp and Rubin is reversed.

CONCLUSION

The rejections of the claims under 35 U.S.C. §102(b) and 35 U.S.C. §103(a) are reversed.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

REVERSED

TONI R. SCHEINER
Administrative Patent Judge

DONALD E. ADAMS
Administrative Patent Judge

DEMETRA J. MILLS
Administrative Patent Judge

) BOARD OF PATENT
) APPEALS AND
) INTERFERENCES

Appeal No. 2002-1930
Application No. 08/478,748

MORGAN & FINNEGAN, LLP
345 Park Avenue
New York, NY 10154

Hawley's

Condensed Chemical

Dictionary

THIRTEENTH EDITION

Revised by

Richard J. Lewis, Sr.

JOHN WILEY & SONS, INC.

New York • Chichester • Weinheim • Brisbane • Singapore • Toronto

This text is printed on acid-free paper. ♾

Library of Congress Cataloging-in-Publication Data

Condensed chemical dictionary.
Hawley's condensed chemical dictionary.—13th ed./revised by
Richard J. Lewis, Sr.
p. cm.
ISBN 0-471-29205-2 (hardcover)
I. Chemistry-Dictionaries. I. Hawley, Gessner Goodrich, 1905–1983.
II. Lewis, Richard J., Sr. III. Title.
QD5.C5 1997
540'.3—dc21 97-35762
CIP

Printed in the United States of America

10 9 8 7 6 5 4

continuous reflux extraction of alcohol- or ether-soluble components of food products. Named after its inventor, a German chemist.

space, chemistry in. Experiments carried out on the space shuttle in the early 1980s indicate that unique types of chemical reactions occur in outer space, and that actual products may result that are not achievable under the terrestrial environment. Several factors are believed to account for this, primarily zero gravity, though absence of oxygen and enhanced magnetic effects may also play a part. Several encouraging results have already been obtained, though until further experiments and operating data have been investigated, the conclusions must be considered tentative. Among projects that have been carried out or are contemplated are the following: (1) Uniform polymer microspheres that are over twice as large as possible on earth have been made due to zero gravity. (2) More effective electrophoresis reactions for making biological materials have been discovered, probably also because of zero gravity. (3) Possibilities exist for (a) making unique alloys in space that are not possible on earth, for example lead-copper, lead-zinc, and aluminum-indium; (b) purer crystals for microelectronics; (c) better glass for fiber optics; (d) new drugs and pharmaceuticals. Future experiments will involve human cells, enzymes, and hormones.

"Spacerite" *[ALCOA].* $Al_2O_3 \cdot 3H_2O$ TM for a spacer pigment of titanium dioxide in coatings and inks.
Properties: White powder.

space velocity. The volume of gas or liquid, measured at specified temperature and pressure (usually standard conditions) passing through unit volume in unit time.
Use: Comparing flow processes involving different conditions, rates of flow, and sizes or shapes of containers.

spalling. Chipping an ore for crushing, or the cracking, breaking, or splintering of materials due to heat.

spandex. Generic name for a fiber in which the fiber-forming substance is a long-chain synthetic polymer composed of at least 85% of a segmented polyurethane (Federal Trade Commission). Imparts elasticity to garments such as girdles, socks, special hosiery.

spanish white. (1) Chalk, $CaCO_3$. (2) Bismuth white, $BiO(NO_3)$, basic bismuth white.

spar. (1) A type of crystalline material such as Iceland spar or feldspar, usually containing calcium carbonate or an aluminum silicate; fluorspar is calcium fluoride. Iceland spar has unique optical properties. (2) A weather-resistant varnish originally used for coating wooden spars of sailing ships, which may be the reason for its name.
See spar varnish.

sparger. A perforated pipe through which steam, air, or water is sprayed into a liquid during a fermentation reaction.
Use: Brewing industry to remove traces of wort from the mash.

spar, Greenland. See cryolite.

spar, heavy. See barite.

spar, Iceland. See calcite.

sparking metal. See pyrophoric alloy.

spar, satin. See calcite; gypsum.

spar varnish. A durable, water-resistant varnish for severe service on exterior exposure. It consists of one or more drying oils (linseed, tung, or dehydrated castor oil), one or more resins (rosin, ester gum, phenolic resin, or modified phenolic resin), one or more volatile thinners (turpentine or petroleum spirits), and driers (linoleates, resinates, or naphthenates of lead, manganese, and cobalt). It is classed as a long-oil varnish and generally consists of 45–50 gals of oil for each 100 lb of resin.
See varnish.

SPE. Abbreviation for Society of Plastics Engineers.

spearmint oil. A yellowish essential oil, strongly levorotatory.
Use: Source of carvone and as flavoring for medicines, chewing gum, etc.

specific activity. (1) The activity of a radioelement per unit weight of the element. (2) The activity per unit mass of a pure radionuclide.

specific gravity. The ratio of the density of a substance to the density of a reference substance; it is an abstract number that is unrelated to any units. For solids and liquids, specific gravity is numerically equal to density, but for gases it is not, because of the difference between the densities of the reference substances, which are usually water (1 g/cc) for solids and liquids and air (0.00129 g/cc, or 1.29 g/L at 0C and 760 mm Hg) for gases. The specific gravity of a gas is the ratio of its density to that of air; since the *specific gravity* of air = 1.0 (1.29/1.29), this is usually stated to indicate the comparison with the gas under consideration. For example, the density of hydrogen is 0.089 g/L but its specific gravity is 0.069 (i.e., 0.089/1.29). The specific gravity of solids and liquids is the ratio of their density

to that of water at 4C, t
weighs 1 gram. Thus a
of 1.5 g/cc has a specif
Since weights of liqui
perature, it is necessar
tures involved, except f
ues. Thus the specific
given as 0.7893 at 20/
ferring to the alcohol a
15.56C the specific gr
See density; API gravity

specification. A sch
mance requirements f
as those established b
the American Society
the Underwriters Lab
subject to inspection
See testing.

specific heat. The
substance to the heat
tity of heat required
change in a unit weig
pressed in Btu/lb/deg
gas the specific heat
than that at constant
needed for expansio

specific susceptibili

specific volume. T
substance, as cubic
pound, but more fr
The reciprocal of d

specific weight. T
substance.

"Spectrograde" *[I*
for potassium brom
CAS: 7758-02-3.
Grade: IR, FTIR, an
Use: IR and FTIR
purity applications.

spectrophotometry
copy.

spectroquality. A
higher purity than
spectrophotometri

spectroscopy. (in
of analytical chem
elements and eluci
structure by measu
sorbed or emitted b
lengths of the elect
to excitation by a
types of absorptio